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14. ABSTRACT

This is the final report on ARO grant W911NF-06-1-0287 titled “Controlled Oligomeric Amphiphiles (COAs)” and dated 1rst July 2006-31rst July 2012. We present a review of our activities during this project, which treats hybrid amphiphiles derived from nucleic acids and lipids. In the latter part of the grant, we developed an example of new encoded aggregates using LONs based aggregates as new responsive drug carrier.

15. SUBJECT TERMS

Amphiphiles, oligonucleotides, lipids, responsive material

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Report Title

Lipid Oligonucleotide conjugates as responsive material

ABSTRACT

This is the final report on ARO grant W911NF-06-1-0287 titled "Controlled Oligomeric Amphiphiles (COAs)" and dated 1rst July 2006-31rst July 2012. We present a review of our activities during this project, which treats hybrid amphiphiles derived from nucleic acids and lipids. In the latter part of the grant, we developed an example of new encoded aggregates using LONs based aggregates as new responsive drug carrier.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received		Paper
2011/10/04 0:	22	Laurent Latxague, Marie-José Dalila, Amit Patwa, Sophia Ziane, Olivier Chassande, Guilhem Godeau, Philippe Barthélémy. . An intrusion into the glycolipids' world? C. R. Chimie, Comptes RendusChimie , (08 2011): 0. doi:
2011/10/04 0:	21	Céballo, C., Khiati, S., Barthélémy, P., Camplo, M., . Acyclic anionic nucleolipids for DNA delivery., Journal of Nanoscience Letters, (07 2012): 20. doi:
2011/05/12 1	17	Amit Patwa, Arnaud Gissot, Isabelle Bestel and Philippe Barthélémy. Hybrid lipid oligonucleotide conjugates: synthesis, self-assemblies and biomedical applications, Chemical Society Review, (05 2011): . doi:
2011/05/12 1	16	Khalid Oumzil, Salim Khiati, Mark W. Grinstaff, Philippe Barthélémy. Reduction-triggered delivery using nucleoside-lipid based carriers possessing a cleavable PEG coating, Journal of Controlled Release , (02 2011): . doi:
2011/05/12 1	15	Guilhem Godeau, Héléne Arnion, Christophe Brun, Cathy Staedel and Philippe Barthélémy. Fluorocarbon oligonucleotide conjugates for nucleic acids delivery, Med. Chem. Commun., (05 2010): . doi:
2011/05/12 1	14	Guilhem Godeau, Christophe Brun, Hélène Arnion, Cathy Staedel, Philippe Barthélémy. Glycosyl-nucleoside ?uorinated amphiphiles as components of nanostructured hydrogels , Tetrahedron Letters, (12 2009): . doi:
2011/05/12 1	13	Claire Ceballos, Carla A. H. Prata, Suzanne Giorgio, Frédéric Garzino, Dominique Payet, Philippe Barthelemy, Mark W. Grinstaff and Michel Camplo. Cationic Nucleoside Lipids Based on a 3-Nitropyrrole Universal Base for siRNA Delivery, Bioconjugate Chem., (12 2008): . doi:
2011/03/01 0	12	Salim Khiati, Nathalie Pierre, Soahary Andriamanarivo, Mark W. Grinstaff, Nessim Arazam, Frederic Nallet, Laurence Navailles, and Philippe Barthelemy. Anionic Nucleotide-Lipids for In Vitro DNA Transfection, Bioconjugate Chemisry, (07 2009): . doi:
2009/03/18 0	9	G. Guilhem, B. Philippe. Glycosyl-Nucleoside-Lipids as Low Molecular Weight Gelators, Langmuir, (2009): . doi:

TOTAL: 9

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

Received		Paper
2009/03/18 0'	8	Louis Moreau, Michel Camplo, Michel Wathier, Nada Taib, Michel Laguerre, Isabelle Bestel, Mark W. Grinstaff, and Philippe Barthelemy*. Real Time Imaging of Supramolecular Assembly Formation via Programmed Nucleolipid Recognition, J. Am. Chem. Soc., (2008): . doi:
2009/03/18 0(	7	Hubert Chapuis, Laurent Bui, Isabelle Bestel, Philippe Barthélémy*. 20-Lipid-modified oligonucleotides via a 'Staudinger–Vilarrasa' reaction, Tetrahedron Letters, (2008): . doi:
2009/03/18 0(	6	Guilhem Godeau, Cathy Staedel, and Philippe Barthelemy*. Lipid-Conjugated Oligonucleotides via "Click Chemistry" Efficiently Inhibit Hepatitis C Virus Translation Virus Translation, J. Med. Chem., (2008): . doi:
2009/03/18 0(	5	Arnaud Gissot, Carmelo Di Primo, Isabelle Bestel, Gregory Giannone, Hubert Chapuis and Philippe Barthelemy*. Sensitive liposomes encoded with oligonucleotide amphiphiles: a biocompatible switch, Chem. Commun., (2008): . doi:
2009/03/18 0(	4	Isabelle Bestel, Nathalie Campins, Alexandr Marchenko, Denis Fichou, Mark W. Grinstaff, Philippe Barthélémy*. Two-dimensional self-assembly and complementary base-pairing between amphiphile nucleotides on graphite, Journal of Colloid and Interface Science, (2008): . doi:
2009/03/17 0'	3	Nathalie Campins, Philippe Dieudonné, Mark W. Grinstaff, and Philippe Barthélémy*. Nanostructured assemblies from nucleotide based amphiphiles, New J. Chem, (2007): . doi:
2009/03/17 0(	2	Philippe Barthelemy. Reprints paper associated with ARO , C. R. Chimie, (2008): . doi:

TOTAL: 7

Number of Papers published in non peer-reviewed journals:

(c) Presentations

1. Philippe Barthélémy, « Hybrid Lipids for Biomedical Applications », Targeting and Triggering Basic Research, ARO symposium, 14-16 May (2012), University of Cambridge, Cambridge, UK, communication.

2. Philippe Barthélémy, « Multfunctional Nanoplatforms for Biomedical Applications », NanoSensorPhotonics 2011, Optical Biosensors, Nanobiophotonics and Diagnostics, Dead Sea, Israel November 5-9, (2011), communication.

3. Philippe Barthélémy, « La biodiversité en territoire indigène : Une corne d'abondance pour la découverte de nouveaux médicaments ? », Indigenous Peoples and the Environment. Dec. 8,9,10th (2011), Bordeaux, France, Invited lecture.

4. Philippe Barthélémy, « Mariage des acides nucléiques avec les lipides : De la chimie moléculaire aux applications biomédicales », Rotary Club, L'Isle sur la Sorgue, Décembre 3, (2011), France, Conférence invitée.

5. Philippe Barthélémy et al. « NAno-plateforme multifonctionnelle dérivée d'Acides Nucléiques » Journées Nationales Nanosciences et Nanotechnologies, Colloque J3N 7-9 novembre (2011) - Palais des congrès de Strasbourg, France, Invited communication.

6. Philippe Barthélémy "Smart" synthetic hybrid lipids for biomedical applications », Biologistes, Chimistes et Physiciens,...aux frontières du vivant, BCP-8, 5th-December (2011), Marseille, France, Invited lecture.

7. Barthélémy P. (invited seminar): "Chimie des systèmes Moléculaires et supramoléculaires à visée Biomédicales", 31rst 2011, Sanofi, Paris, France.

8. Barthélémy P. (invited lecture): « AUTO-ASSEMBLAGES ET APPLICATIONS BIOMÉDICALES » University of Grenoble, 12th April (2011), France.

9. Barthélémy P. (invited seminar): "Bioinspired hybrid amphiphiles: when lipids met nucleic acids...", Nucleic acid center (NAC), Odense 15th/06/2011, Denmark.

10. A. Aimé, A. Patwa, X. Moreau, L. De Jong, G. Saez, C. Di Giorgio, M. De Méo, Thiéry, I. Bestel P. Barthélémy (poster): "“NANAN" - A multifonctional oligonucleotide-based nanoplatform", SUPRABIO, October 2010, Bordeaux, CRPP, France.

11. N. Taib, A. Aimé, M. Laguerre, P. Barthélémy, I. Bestel (poster): "Molecular modeling of nucleolipids base-pairing interactions", SUPRABIO, October 2010, Bordeaux, CRPP, France.

12. Barthélémy P. (invited lecture): « AMPHIPHILES HYBRIDES DÉRIVÉS DE BIOMOLÉCULES: AUTO-ASSEMBLAGES ET APPLICATIONS BIOMÉDICALES » University of Montpellier 2, School of Chemistry 18th November (2010), France.

13. Barthélémy P. (invited lecture): "Smart" Lipids for Biomedical Applications, 9th France-Japan Drug Delivery System (DDS) Symposium, 26-29, 2010. Kumamoto, Japan.

14. Barthélémy, P. (oral communication): « GLYCOSYL-NUCLEOSIDE-LIPID BASED SUPRAMOLECULAR MATERIALS; A "MENAGE A TROIS" FOR BIOMEDICAL APPLICATIONS », XIX International Round Table on Nucleosides, Nucleotides and Nucleic Acids Lyon, France - 29 August - 3 September 2010.

15. Laetitia De Jong-Moreau, Xavier Moreau, Gladys Saez, Alain Thiéry, Isabelle Betsel, Aime Ahissan, Philippe Barthélémy (poster): "Are nanoparticles encapsulated with nucleolipids safe for freshwater invertebrates?" SUPRABIO, October 2010, Bordeaux, CRPP, France.

16. Delphine Luvino, Salim Khiati, Frédéric Garzino, Alain Méou, Philippe Barthélémy, Michel Camplo, (poster): "Original cationic nucleoside lipid for gene delivery" SUPRABIO, October 2010, Bordeaux, CRPP, France.

17. Barthélémy P. (invited lecture): « Hybrid bioinspired amphiphiles: from supramolecular chemistry to biomedical applications » Southampton Supramolecular Chemistry Symposium - 7, 16th July (2010), University of Southampton, UK.

18. Barthélémy P. (invited lecture): « NanoBiotechnology/ Nanomedicine », NanoSpain CONF2010, March 26th (2010) Malaga, Spain.

19. Barthélémy, P. (oral communication): « Nanostructured materials for drug delivery », Rencontres en Chimie Organique Biologique,

(RECOB13) 21-25th March (2010), Aussois, France.

20. Barthélémy P. (invited seminar): Nucléolipides ; auto-assemblages et applications biomédicales. Nancy, June (2010), Université Henri Poincaré-Nancy I, France.

21. Luvino D., Ceballos, C., Khiati S., Garzino F., Méou A., Barthélémy P., and Camplo, M., (poster) : "Synthèse de nouvelle molecules hybride dérivée de nucleosides amphiphiles cationiques" Rencontres en Chimie Organique Biologique, (RECOB13) 21-25th March (2010), Aussois, France.

22. Khiati, S.; Luvino, D.; Oumzil, K.; Pierre, N.; Camplo, M.; Chauffert, B.; Barthélémy, P. (poster): Nanoparticles vectors for drugs delivery - Cancéropôle Grand Sud-Ouest, 1rst July (2010), Toulouse, France.

23. K. Oumzil, S. Khiati, P. Barthélémy (poster): Nucléolipides PEG-détachables pour la vectorisation - Cancéropôle Grand Sud-Ouest, 1rst July (2010), Toulouse, France.

24. P. Barthélémy (oral communication): “Nanostructured hydrogels for nucleic acid delivery” GTRV- Summer School, « Targeted drug delivery » September 3-4, (2009), EPFL (Polydôme), Lausanne, Switzerland.

25. Godeau, G. ; Steadel C. ; Pierre, N. ; Barthélémy, P. : Oligonucléotides lipidiques : Journées Jeunes Chercheurs SCT, Paris, le 5 février 2009, France

26. Godeau, G.; Bernard, J.; Staedel, C.; Barthélémy, P. Glycosyl-Nucleoside-Lipids as Low molecular weight Gelators. 10th scientific day of the doctoral school sciences of life and health, Arcachon (France), 8 April 2009, France

27. Godeau, G. ; Steadel C. ; Pierre, N. ; Barthélémy P. : Oligonucléotides amphiphile : un nouvel outil de vectorisation. GTRV, Angers, le 8 décembre 2008, France

28. Godeau, G. ; Steadel C. ; Pierre, N. ; Barthélémy, P. : Oligonucléotides amphiphile : Journée Scientifique de l'IFR 66, Talence, le 2 décembre 2008, France

29. Taib N.; Berque-Bestel I.; Laguerre M.; Barthélémy, P. Nucleoside amphiphiles for intracellular delivery of antisenses targeting exon associated with muscular distrophy. GTRV, Angers, le 8 décembre 2008, France.

30. Gissot A., Diprimo C. ; Berque-Bestel, Giannone G. Chapuis H..; Barthélémy, P. . New biocompatible switch for sensitive liposomes encoded with oligonucleotides amphphiles. GTRV, Angers, le 8 décembre 2008, France.

31. Chapuis, H.; Bui, Laurent, Pierre, N.; Staedel, C.; Berque-Bestel, I. Barthélémy, P. Ciblage de micorARNs par des oligonucléotides amphiphhiles à visée thérapeutique 4ème journée nationale du Club "Nanomatériaux pour les Sciences du Vivant" intitulée : Vectorisation de Molécules Actives et Ciblage Biologique le 27 mars 2008 à ENSCPB (Bordeaux, France)

32. Bui, L.; Chapuis, H.; Pierre, N.; Staedel, C.; Berque-Bestel, I.; Barthélémy, P. 44e Rencontres Internationales de Chimie Thérapeutique intitulées “*Interfacing Chemical Biology, Natural Products and Drug Discovery*” in Angers (France) on July 2-4, 2008.

33. S. Khiati, N Campins, N Pierre, P Barthélémy. Club Nanomatériaux pour les sciences du Vivant, 4ème rencontre, Vectorisation de molécules actives et ciblage biologique, Bordeaux 27 mars 2008, ENSCPB.

34. S. Khiati, N Campins, N Pierre, P Barthélémy. Interface Chimie - Biologie – Physique, 1ère Journée Jeunes Chercheurs, Bordeaux 22 Mai 2008. IECB.

35. S. Khiati, N Campins, N Pierre, P Barthélémy. Journée Doc's meeting 66, Bordeaux Mardi 24 JUIN, 2008. ENSCPB.

Number of Presentations: 35.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received		Paper
2009/03/18 0'	11	Khiati Salim, Pierre Nathalie, Grinstaff Mark W., Navailles Laurence, Barthélémy Philippe*. Anionic nucleotide-lipids for in vitro DNA transfection, Bioconjugate Chemisry (2009)
2009/03/18 0'	10	Guilhem Godeau, Julie Bernard, Cathy Staedel and Philippe Barthélémy*. Glycosyl-nucleoside-lipid based supramolecular assembly as a nanostructured hydrogel material with Nucleic acid delivery capabilities**, Angewandte Chemie (2009)

TOTAL: **2**

Number of Manuscripts:

Books

Received Paper

TOTAL:

Patents Submitted

Patents Awarded

Awards

Graduate Students

NAME	PERCENT_SUPPORTED	Discipline
Salim Kiathi	0.30	
FTE Equivalent:	**0.30**	
Total Number:	**1**	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
Amit Patwa	0.20
Khalid Oumzil	0.40
alex Pokholenko	0.80
Hubert Chapuis	0.80
FTE Equivalent:	**2.20**
Total Number:	**4**

Names of Faculty Supported

NAME	PERCENT_SUPPORTED	National Academy Member
Arnaud Gissot	0.20	No
Isabelle Bestel	0.20	
Laurent Latxague	0.20	
FTE Equivalent:	**0.60**	
Total Number:	**3**	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED	Discipline
Christophe Brun	0.20	Biosciences
FTE Equivalent:	**0.20**	
Total Number:	**1**	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period: 1.00

The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:...... 0.00

The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:...... 0.00

Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):...... 0.00

Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:...... 0.00

The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense 0.00

The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:...... 0.00

Names of Personnel receiving masters degrees

NAME	
Total Number:	

Names of personnel receiving PHDs

NAME	
Salim Khiati	
Total Number:	**1**

Names of other research staff

NAME	PERCENT_SUPPORTED
Brune Vialet	0.10
FTE Equivalent:	**0.10**
Total Number:	**1**

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

See Attachment

Technology Transfer

Final Report

(July 1rst 2006 to July 31rst, 2012)

Proposal title: Controlled Oligomeric Amphiphiles (COAs)

Contract W911NF-06-1-0287

Report title: Lipid Oligonucleotide conjugates as responsive material

Author: P. Barthélémy

Abstract

This is the final report on ARO grant W911NF-06-1-0287 titled "Controlled Oligomeric Amphiphiles (COAs)" and dated 1rst July 2006-31rst July 2012. We present a review of our activities during this project, which treats hybrid amphiphiles derived from nucleic acids and lipids. In the latter part of the grant, we developed an example of new encoded aggregates using LONs based aggregates as new responsive drug carrier.

Table of Contents

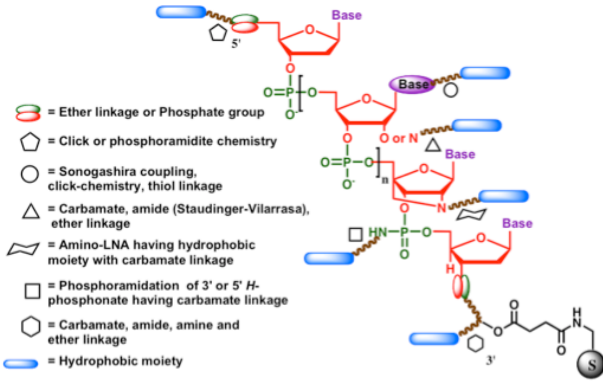
In this report we summarize the results collected from the beginning of this contract. After a short introduction on hybrid lipid oligonucleotides, we present the study of the LON aggregates obtained with LONs synthetized in our lab after solubilization in aqueous samples. Also, we present the use of the LONs as responsive materials for drug delivery applications.

Introduction

Lipids OligoNucleotides conjugates (LONs) are attracting attention owing to their unique physicochemical and biological properties. These amphiphiles, which feature molecular recognition capabilities, have been reported to self assemble into different aggregates including micelles, liposomes and nanoparticles.[1] LONs have been also developed for biomedical applications and novel therapeutic strategies.[2]

Design and synthesis. The development of synthetic methods for the preparation of LONs is an important step to the access of these amphiphiles. Scheme 1 describes the possible ways of hydrophobic conjugations to the different moieties of oligonucleotide (i. e. at sugar, phosphate backbone or base unit). Hydrophobic part can be lipid (LONs) or fluorinated alykyl chain (FONs)[3] or any other surfactant (DNAsurf.). Organic chemistry and solid phase synthesis (SPS) are unavoidable expertises required for the synthesis of LONs. Two general strategies exist for the incorporation of simple hydrophobic modification(s) anywhere (Figure 1a) in the sequence of the oligonucleotides, called presynthetic and postsynthetic approach (Figure 2b and 2c).

Presynthetic approach denotes that the nucleotide monomers already carry the desired hydrophobic moiety before oligonucleotide synthesis, deprotection, and purification. That is, these modified nucleotides are incorporated into the oligonucleotide sequence during the usual phosphoramidite process. Post synthetic labelling requires the introduction of a small reactive moiety into oligonucleotide, which can be coupled to the hydrophobic part after completion of oligonucleotide synthesis.



Scheme 1. Schematic representation for LONs showing different sites of hydrophobic conjugations.

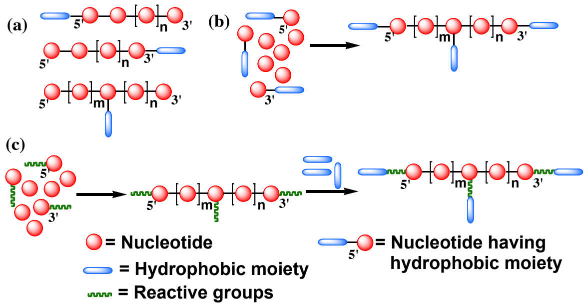


Figure 1. Schematic representation for (a) LON structures (Hydrophobic moieties can be incorporated either at the termini (3'- and/or 5') or within the oligonucleotide sequence) (b) presynhetic approach (c) postsynthetic approach.

Self-assemblies. Different strategies have been developed for the introduction of one or several hydrophobic motifs to oligonucleotides. Obviously, the lipophilic segments confer amphiphilic as well as self-aggregation properties to the resulting LONs. Basically, LONs can be regarded as disymmetric, double-sided scotch tapes with 1) a poorly specific lipidic glue side that allows for the self-association and/or insertion of LON into membranes associated with 2) an oligonucleotidic smart side responsible for the specific recognition of defined targets (oligonucleotides or others). The synergy between the

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[1] A) H. Liu, Z. Zhu, H. Kang, Y. Wu, K. Sefan, and W. Tan, *Chem. Eur. J.*, 2010, **16**, 3791. B) M. P. Thompson, M.-P. Chien, T.-H. Ku, A. M. Rush, and N. C. Gianneschi, *Nano Lett.*, 2010, **10**, 2690. C) F. Gambinossi, M. Banchelli, A. Durand, D. Berti, T. Brown, G. Caminati, and P. Baglioni, *J. Phys. Chem. B.*, 2010, **114**, 7338.

[2] A) A. Gissot, M. Camplo, M. W. Grinstaff, and P. Barthélémy, *Org. Biomol. Chem.*, 2008, **6**, 1324. B) C. Mao, T. H. LaBean, J. H. Reif, and N. C. Seeman, *Nature*, 2000, **407**, 493. C) N. Bowden, A. Terfort, J. Carbeck, and G. M. Whitesides, *Science*, 1997, **276**, 233. D) M. Lee, C.-J. Jang, and J.-H. Ryu, *J. Am. Chem. Soc.*, 2004, **126**, 8082. E) A. Petitjean, R. G. Khoury, N. Kyritsakas, and J.-M. Lehn, *J. Am. Chem. Soc.*, 2004, **126**, 6637. F) G. M. Whitesides, J. P. Mathias, and C. T. Seto, *Science*, 1991, **254**, 1312. G) J. Krützfeldt, N. Rajewsky, R. Braich, K. G. Rajeev, T. Tuschl, M. Manoharan, and M. Stoffel, *Nature*, 2005, **438**, 685.

[3] G. Godeau, H. Arnion, C. Brun, C. Staedel, and P. Barthélémy, *Med. Chem. Commun.*, 2010, 1, 76

mode of recognition of the lipid and the oligonucleotide is central in the many recent applications of LONs published lately.

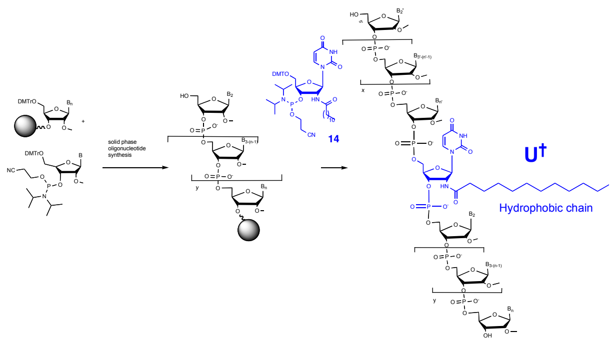
Biomedical applications. Successful biomedical applications based on the administration of LONs *in vivo* are mostly dedicated to the field of RNA interference (RNAi). Following the discovery of RNAi as a means to silence expression of specific genes involved in disease, new gene therapy strategies were developed. The two key actors of the RNAi pathway, which are the targets of new RNAi-based therapeutics are small interfering RNA (siRNAs) and microRNA (miRNA). Despite similarities in their silencing pathways, including a common loading into a protein complex called the RNA induced silencing complex (RISC), the modes of action of these molecules present differences. Both siRNA and miRNA target mRNA, acting as post-transcriptional regulators. The success of siRNA and miRNA-based therapeutics in in vitro studies has recently prompted the development of i*n vivo* investigations. Nevertheless *in vivo* delivery remains one of the major obstacle of this therapeutic strategy stimulating the active research of vector-based delivery system. In this context LONs have successfully been used to silence gene expression in mice and in non-human primates.[4]

During this programme we have developed synthetic pathways to prepare new LON derivatives. We have investigated their aggregation behaviors and studied their biological/therapeutic properties. In the next sections we summarize the most important results.

2/ Summary of the most important results

Synthetic access to LONs. The synthesis of the first LONs dates back to the late 80's, early 90's and is closely associated with the outbreak of the antisense strategy for gene therapy.[5] The basic idea underlying the synthesis of these molecules was to provide an anchor for the antisense oligonucleotide into the membrane thus facilitating internalization of the oligonucleotide. Within the framework of this programme we have been interested in both studying the aggregation properties of LONs and developing new biologically relevant sequences. Basically three different synthetic strategies have been developed in the lab for the preparation of LONs.

The first LON sequences, selected for in this part of the project, are antisense of mirR-122, which belong to the antagomir's approach.[6] A LON also named controlled oligomeric amphiphiles (COAs) having a complementary sequence of miR-122 was first synthesized (Figure 2). For that purpose a new access to 2'-amido-2'-deoxyuridine via a Staudinger–Vilarrasa coupling reaction was developped. One or two lipidic moieties were inserted within the oligonucleotidic sequence (LONs) leading to a repertoire of original antagomir-like molecules targeting micro RNA (miRNA or miR). A second type of LON conjugates was also prepared in three steps starting from alkyne-modified lipids derived from cholesterol and octadecanol (see publication ***21*** for details). Briefly, 5′-azido-5′-deoxythymidine was refluxed with propargyl lipids in water/THF. The resulting 1,3-dipolar cycloaddition reaction provided the expected 1,2,3-triazole intermediates, which were converted into the phosphoramidites in one step and further coupled to the ON chain using a classical solid support



2'-OMe(CAAACACCAU U†GUCACACUCCA)

Figure 2. Up, Solid phase synthesis of a COA featuring a hydrophobic chain incorporated in the oligonucleotide sequence. Down, oligonucleotide sequence selected in this project (complementary to miR-122). See publication ***23*** for détails.

[4] a) L. Ma, F. Reinhardt, E. Pan, J. Soutschek, B. Bhat, E. G. Marcusson, J. Teruya-Feldstein, G. W. Bell, and R. A. Weinberg, *Nat. Biotechnol.*, 2010, **28**, 341. B) Q. Chen, D. Butler, W. Querbes, R. K. Pandey, P. Ge, M. A. Maier, L. Zhang, K. G. Rajeev, L. Nechev, V. Kotelianski, M. Manoharan, and D. W. Y. Sah, *J. Controlled Release*, 2010, **144**, 227. C) M. DiFiglia, M. Sena-Esteves, K. Chase, E. Sapp, E. Pfister, M. Sass, J. Yoder, P. Reeves, R. K. Pandey, K. G. Rajeev, M. Manoharan, D. W. Y. Sah, P. D. Zamore, and N. Aronin, *Proc. Natl. Acad. Sci. U.S.A.*, 2007, **104**, 17204. D) W. Querbes, P. Ge, W. Zhang, Y. Fan, J. Costigan, K. Charisse, M. Maier, L. Nechev, M. Manoharan, V. Kotelianski, and D. W. Y. Sah, *Oligonucleotides*, 2009, **19**, 23.

[5] C. Wilson and A. D. Keefe, Curr Opin Chem Biol, 2006, 10, 607-614. I. Pfeiffer and F. Hook, *J. Am. Chem. Soc*., 2004, 126, 10224-10225. I. Pfeiffer and F. Hook, Anal Chem, 2006, 78, 7493-7498.

[6] Krutzfeldt J, Rajewsky N, Braich R, Rajeev KG, Tuschl T, Manoharan M, Stoffel M. Silencing of microRNAs in vivo with 'antagomirs'. *Nature*. 2005 Dec 1;438(7068):685-9.

synthesis. A similar strategy of functionalization was also used for the incorporation of fluorocarbon chain at the 5' ON end (see publication ***11*** for details). The third family of amphiphiles developed was synthetized from double chain ketal phosphoramidite inserted at the 5' extremity during the ON synthesis (see publication ***22*** for details).

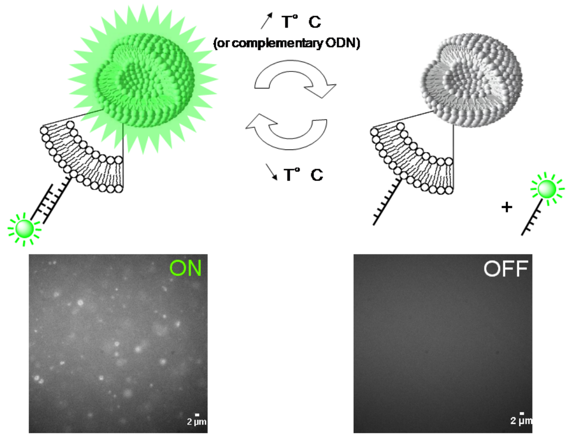


Figure 3. DNA-tagged liposomes switch between an on and off fluorescent state depending on an external stimulus, either physical (temperature) or chemical (competitive complementary ON sequences). Both the platform and the switch are biocompatible. See publication ***22*** for détails.

LONs in supramolecular assemblies. The unique recognition properties of oligonucleotidic headgroup associated with these amphiphiles make LONs appealing building blocks for supramolecular applications. The supramolecular behaviors of the LONs in the absence of lipids have been investigated on several systems; including a 17mer polyUridine featuring an octadecyl saturated chain and a 5'-cholesterol 17mer derivative. Interestingly, we discovered that LONs self-assemble to give spherical nano-objects. One of the objectives of this program was devoted to the characterization of the nanoparticles obtained. In many cases micellar systems were observed (unpublished data, see last section). Also relevant to this programme was the development of liposome-based nanoplatform wherein liposomes were tagged with LONs (Figure 3). It was found that such platform allowed for the straightforward recognition and detection of the oligonucleotide complementary to the oligoamphiphiles present at the surface of the liposome. Liposomes were thus switch on and off in response to either the presence of the targeted nucleic acid or temperature switch. Importantly, surface plasmon resonance (SPR) studies indicated that the kinetics of duplex formation at the surface of the liposomes remained essentially unaffected when compared to the formation of the same duplex free in solution. These proof-of-principle investigations demonstrate that recognition events are feasible and are essentially unaltered at the surface of membrane bilayers.

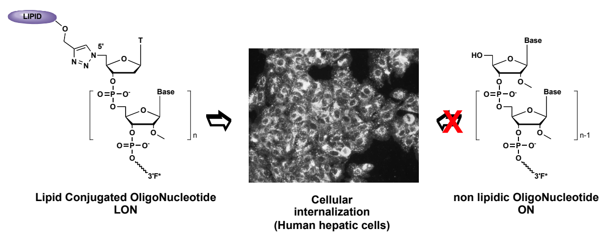


Figure 4. Conjugation of a lipid moiety *via* 'click chemistry' potentiates the cellular uptake of oligonucleotides and allows their intracellular delivery. These non-toxic lipid-conjugates efficiently inhibit hepatitis C virus IRES-mediated translation in Human hepatic Huh7 cells. The biological activity of the lipid-conjugated oligonucleotides is not affected by the presence of serum. See publication ***21*** for détails.

Biological activities: In terms of biological activities, results collected have shown that the incorporation of a lipid moiety *via* a non-scissile triazole linker potentiates the cellular uptake of the oligonucleotides and affords an increase in ON delivery as measured by fluorescence microscopy and flow cytometry. Lipid-conjugated induced a dose-dependent reduction of HCV IRES-dependent translation in Huh7 cell line (Figure 4). More importantly, toxicity of the lipid-oligonucleotide conjugates was negligible and biological activity of the ONAs was not affected by the presence of serum (see publication ***21*** and ***7*** for details). In this programme we also developped an automated synthetic pathway for the synthesis of fluorocarbon oligonucleotide conjugates (FONs) featuring fluorocarbon hydrophobic and lipophobic moieties (see publications ***11*** and ***2*** for details). The presence of highly fluorinated chains allows the delivery of nucleic acids into human cells.These results will have important implications on the future design of cell-permeable oligonucleotides, including antisenses, antagomirs, siRNA or aptamers.

In parallel to LONs and FONs, we also developed new nucleoside nucleotide amphiphiles to allow the cellular internalization of ON sequences. For that purpose we designed different low molecular weight molecules, including nucleotide lipids, glycosylated nucleolipids and pegylated derivatives, for example.

- *Nucleotide lipids.* A family of new anionic nucleotide based lipids featuring thymidine-3′-monophosphate as nucleotide and 1,2-diacyl-sn-glycerol as lipid moiety for in Vitro delivery of nucleic acids was first reported (See publications ***4***, ***17*** and ***18*** for details). The nucleotide lipids (Figure 5) were prepared in three steps starting from 1,2-diacyl-sn-glycerols and 2′-deoxythymidine-3′-phosphoramidite. Gel electrophoresis experiments showed that nucleotide-based lipid-DNA complexes are observed at Ca^{2+} concentration higher than 1 mM. The transfection experiments carried out on mammalian Hek cell lines clearly demonstrate that the nucleotide moiety enhances the transfection efficacy of the natural anionic DPPA and DPPG lipids.

SAXS studies indicate that the enhancement in transfection for nucleotide-based lipid formulations compared to those of the abasic natural derivative (DPPA) is likely due to the presence of the 2D columnar inverted hexagonal phase (HII). The cytotoxicity studies of lipoplexes, evaluated against Hek cells using an MTS assay, revealed that palmitoyl nucleotide derivative complexes were not toxic even after 4 h of incubation, thus indicating that the anionic nucleotide lipids presented in this work offer an alternative to cationic transfection reagents.

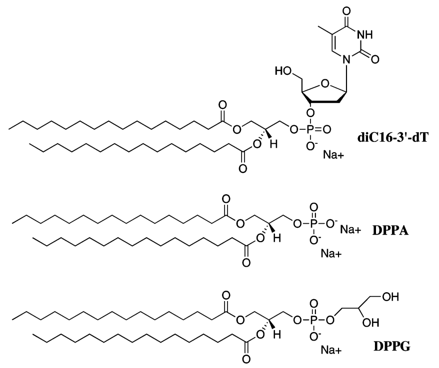


Figure 5. Chemical Structure of an Anionic Nucleotide-Lipid Used in This Study, the Thymidine 3′-(1,2-dipalmitoyl-sn-glycero- 3-phosphate) (di c16dT) and Non-Nucleotide-Lipids DPPA and DPPG. See publication***18*** for détails.

- *Glycosylated nucleolipids (GNLs)*.

In this part of the work we have developed a new family of LMWG. We discovered that these fully tunable compounds are able to form nanostructured hydrogel in water and to complex nucleic acids. Our studies also demonstrated that the nucleic acid/GNL complex increase the cellular uptake in presence of serum and without toxicity. The addition of the tuning potential and the ability to transfer nucleic acids of the GNL illustrate the great potential of thus structures (Figure 6). Note that fluorocarbon analogues (GNFs) were also synthesized in this part of the programme (See publications ***13*** for details).

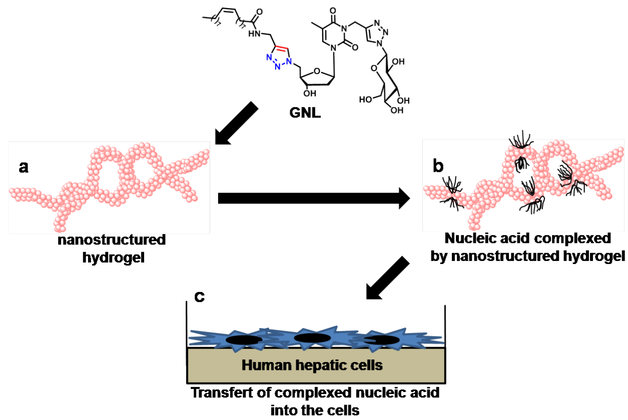


Figure 6. Schematic representation of the nanostructured hydrogel formed by the GNL in water (a). These suppramolecular assemblies are able to complex nucleic acids (b) and to increase the oligonucleotide transfer into human cells(c). See publications ***14*** and ***15*** for détails.

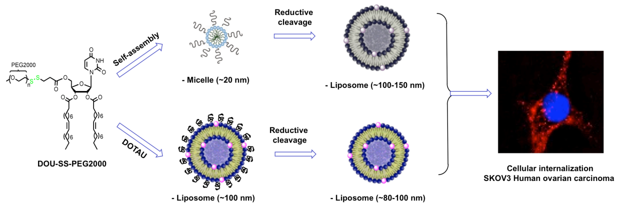


Figure 7. A new non-ionic nucleoside based lipid (DOU-SS-PEG2000, 5'-PEG2000-2',3'-dioleoyluridine) featuring uridine (U) as nucleoside and 2',3'-dioleyl (DO), as lipid moieties and a poly(ethylene glycol) (PEG) thiolytic cleavable spacer for in vitro delivery of drugs is described. The reduction-triggered delivery using the PEG detachable nucleoside lipid DOU-SS-PEG2000 was evaluated on both liposomal and micellar objects. Note that the supramolecular systems underwent a reduction-induced morphology transition from a micellar to vesicular states. See publications ***8*** for détails.

- *Cleavable pegylated derivatives*. The issue of PEGylation is particularly important in protocols that attempt to deliver *in vivo* stealth nano-objects. To address this issue, a DOU-SS-PEG_{2000} nucleolipid proposed in this part of the programme offers an alternative to current pegylated species. Thus, we synthesized a PEG detachable nucleoside based lipid (DOU-SS-PEG_{2000}, 5'-PEG_{2000}-2',3'-dioleoyluridine) featuring uridine (U) as nucleoside and 2',3'-dioleyl (DO), as lipid moieties and a poly(ethylene glycol) (PEG) thiolytic cleavable spacer for in vitro cellular delivery. The PEG detachable nucleotide lipid (DOU-SS-PEG_{2000}) was prepared *via* a convergent synthesis starting from HS-PEG-OMe and uridine. The reduction-triggered delivery system based on the DOU-SS-PEG_{2000} was investigated on both liposomes and micelles. DOU-SS-PEG_{2000} self organized to give micelles of 20 nm in diameter. DLS, zeta potential and TEM investigations on DOU-SS-PEG2000 supramolecular systems demonstrate that a reduction-induced morphology transition occurs from a micellar to vesicular states. In the case of liposomes, the disulfide bond of the PEG chain was cleaved to display the cationic surface of the "naked" liposome in reduction conditions. Cleavage of the disulfide bond of PEG chains in the presence of DTT results in an enhanced cellular internalization of both micelles and liposomes in ovarian cancer cell line SKOV3. These results show that using a PEG detachable nucleoside-lipid in formulations to optimize internalization efficacy.

3/ LONs as responsive materials for drug delivery applications

To design new drugs and drug delivery systems (DDS), chemists operate by molecular shape complementarity, hydrogen bondings, charge and/or dipole interactions, covalent bonding and hydrophobic effects as means of binding healing molecules to their malfunctioning targets. Oligonucleotides are placed on the scene of drugs these days, but these molecules could also be used as new DDS.

Basically, oligonucleotides function in a living organism *via* supramolecular aggregation, mostly Watson-Crick complementary base pairing. Supramolecular complexes of polynucleotides are stabilized first of all because of hydrogen bonds that are formed due to molecular shape matching between classical complementary nucleobases (Watson-Crick pairing), non-classical Hoogsteen pairing (Adenine-Thymidin/Uracil), Adenin-Guanin pairing, triple complexes (T•AT, C•GC, G•GC), guanine quadruplexes. After base pairs are formed, pi-stacking interactions contribute to further stabilization. The conjugation of lipid molecules to these biopolymers (lipid oligonucleotides, LONs) could open new horizons in the design of both drugs and new advanced DDS. Introducing hydrophobic chains into the molecular structure of oligonucleotides could lead to the formation of supramolecular complexes, which could play two roles: induce the self-vectorization of a biological relevant sequences and load hydrophobic drugs in their lipidic reservoir for delivery purpose.

To explore this conceptual approach we have designed and prepared several oligonucleotides bearing lipophilic tails. In this part of the programme we synthesized LONs featuring double and triple lipophilic chains (figure 8). We found that these LONs self-assemble into micelles, which are prone to host paclitaxel molecules within their hydrophobic cores. Our results demonstrate that the composition of the LONs both in terms of the lipid and the oligonucleotide sequence impact their ability to host lipophilic molecules. Interestingly, the drug intake of ^{2}LON-A_{15} was markedly high compared to other LONs. It was found that the polyA sequence serves three roles: (1) it promotes the transfer of the alkyl chains of the LONs into water, (2) it potentializes the drug intake of the LON aggregates and (3) it can hydridize with the cDNA sequence to trigger the release of the drug. Only two oligonucleotide sequences (dA15 and dT15) have been investigated in this study. Consequently, there is still space for further optimization of the ON length and composition.

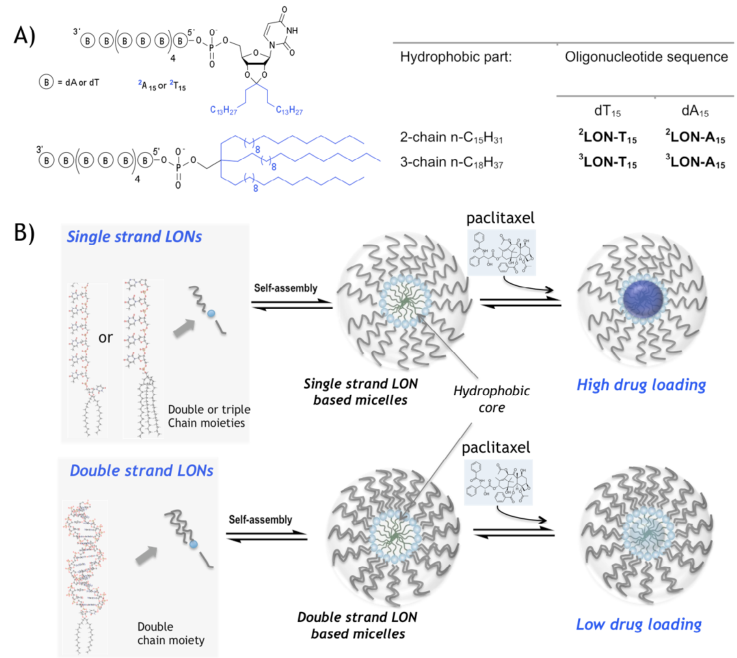


Figure 8. A) Double and triple chain LONs synthetized in this study. B) Schematic representation of single and double strand LON based micelles loaded with an antitumoral drug: Paclitaxel.

Numerous stimuli-bioresponsive drug delivery systems have been developed to induce the release of the drug in response to certain stimuli like pH, temperature, redox potential, enzymes, light, and ultrasound. In this work we demonstrate for the first time that the **drug loading of LON based nanomaterials can be modulated *via* complementary oligonucleotide stimulus.** LON aggregates afford an original and specific stimuli-bioresponsive alternative to address the drug controlled delivery issue. We hope this oligonucleotide-based strategy for the formulation of lipophilic drugs will find other applications in the realm of drug delivery.

4/ Peer review papers published that acknowledge ARO during this reporting time

1. Taïb, N.; Aimé, A.; Moreau, L.; Camplo M.; Houmadi, S.; Desbat B.; Laguerre M.; Grinstaff, M.; Bestel I. and Barthélémy P. (**2012**) Formation of Supramolecular Systems via Directed Nucleoside-lipid Recognition, *J. Colloid Interface Science*, 1;377(1):122-30.

2. Dolain, C.; Patwa, A.; Godeau, G.; Barthélémy, P. (**2012**) "Nucleic Acid Based Fluorinated Derivatives: New Tools for Biomedical Applications." *Appl. Sci.* 2, 245-259.

3. Latxague, L., Dalila, M.J., Patwa, A. Sophia, Z., Chassande, O., Godeau, G. and Barthélémy P. (**2012**) Glycoside nucleoside lipids (GNLs): An intrusion into the glycolipids' world? *C.R.Chimie*, 15, 29–36

4. Céballo, C., Khiati, S., Barthélémy, P., Camplo, M., (**2012**) Acyclic anionic nucleolipids for DNA delivery. *J. Nanosci. Lett.*, 2: 20

5. Laurent Latxague, Sophia Ziane, Olivier Chassande, Amit Patwa, Marie-José Dalila and Philippe Barthélémy, (**2011**) Glycosylated nucleoside lipid promotes the liposome internalization in stem cells, *Chem. Commun.*, DOI: 10.1039/c1cc13948g.

6. Laurent Latxague, Marie-José Dalila, Amit Patwa, Sophia Ziane, Olivier Chassande, Guilhem Godeau, Philippe Barthélémy. Glycoside nucleoside lipids (GNLs): An intrusion into the glycolipids' world? *C. R. Chimie* (**2011**), doi:10.1016/j.crci.2011.08.010

7. Patwa, A., Gissot, A., Bestel, I., and Barthélémy, P. (**2011**) Hybrid lipid oligonucleotide conjugates: synthesis, self-assemblies and biomedical applications. *Chem. Soc. Rev.*, DOI: 10.1039/C1CS15038C.

8. Oumzil, K., Khiati, S., Grinstaff, M. W., and Barthélémy, P. (**2011**) Reduction-triggered delivery using nucleoside-lipid based carriers possessing a cleavable PEG coating. *J. Control. Release*, doi:10.1016/j.jconrel.2011.02.008

9. Zhang, X.-X., Prata, C., McIntosh, T., Barthélémy, P. and Grinstaff, M. (**2011**) Synthesis, Characterization, and In Vitro Transfection Activity of Charge-Reversal Amphiphiles for DNA Delivery. *Bioconjug. Chem*., 22, 690–69.

10. Zhang, X.X., Prata, C.A., McIntosh, T.J., Barthélémy, P., Grinstaff, M.W. (**2010**) The effect of charge-reversal amphiphile spacer composition on DNA and siRNA delivery. *Bioconjug. Chem.* 21, 988-993.

11. Guilhem Godeau, Héléne Arnion, Christophe Brun, Cathy Staedel and Philippe Barthélémy (**2010**) Fluorocarbon oligonucleotide conjugates for nucleic acids delivery. *Med. Chem. Commun*., 1, 76–78

12. Ceballos, C., Khiati, S., Prata, C.A., Zhang, X.X., Giorgio, S., Marsal, P., Grinstaff, M.W., Barthélémy, P., Camplo, M. (**2010**) Cationic nucleoside lipids derived from universal bases: A rational approach for siRNA transfection. *Bioconjug. Chem.* 21, 1062-1069.

13. Godeau, G., Brun C., Arnion, H., Staedel, C., Barthélémy, P. (**2010**) "Glycosyl-nucleoside fluorinated amphiphiles as components of nanostructured hydrogels" *Tetrahedron Letters*, (51), 1012-1015

14. Godeau, G., J. Bernard, Staedel, C. and Barthélémy, P. (**2009**). "Glycosyl–nucleoside–lipid based supramolecular assembly as a nanostructured material with nucleic acid delivery capabilities." *Chemical Communications* 34: 5127 – 5129.

15. Godeau, G. and Barthélémy P. (**2009**). "Glycosyl-Nucleoside-Lipids as Low Molecular Weight Gelators." *Langmuir* 25: 8447-8450

16. Ceballos, C., Prata, C. A. H. Giorgio, S. Garzino, F. Payet, D. Barthélémy, P. Grinstaff, M. W. Camplo, M. (**2009**). « Cationic nucleoside lipids based on a 3-nitropyrrole universal Base for siRNA delivery. » *Bioconjugate Chemistry* 20(2): 193-196.

17. Barthélémy, P. (**2009**). «Nucleoside-based lipids at work: From supramolecular assemblies to biological applications. » *Comptes Rendus Chimie* 12(1-2): 171-179.

18. Salim Khiati, Nathalie Pierre, Soahary Andriamanarivo, Mark W. Grinstaff,| Nessim Arazam, Frédéric Nallet, Laurence Navailles, and Philippe Barthélémy (**2009**) « Anionic Nucleotide-Lipids for In Vitro DNA Transfection » *Bioconjugate Chemistry*, (20), 1765-1772.

19. Moreau, L. ; Camplo, M. ; Wathier, M. ; Taib, N. ; Laguerre, M. ; Bestel, I. ; Grinstaff, M. W. ; and Barthélémy, P. (**2008**). "Real time imaging of supramolecular assembly formation via programmed nucleolipid recognition." *Journal of the American Chemical Society* 130(44): 14454-14455.

20. Bestel I, Campins N, Marchenko A, Fichou D, Grinstaff MW, Barthélémy P. « Two-dimensional self-assembly and complementary base-pairing between amphiphile nucleotides on graphite. » *J Colloid Interface Sci.* (**2008)** Jul 15;323(2):435-40.

21. Guilhem Godeau, Cathy Staedel, and Philippe Barthélémy « Lipid-conjugated oligonucleotides via "click chemistry" efficiently inhibit hepatitis C virus IRES-mediated translation », *J. Med. Chem.* (**2008)**, 51, 4374-6.

22. Arnaud Gissot, Carmelo Di Primo, Isabelle Bestel, Gregory Giannone, Hubert Chapuis and Philippe Barthélémy « Sensitive liposomes encoded with oligonucleotide amphiphiles: a biocompatible switch » *Chem. Commun.* (**2008)**, (43), 5550-2.

23. Chapuis, H.; Bui, L.; Bestel, I.; Barthélémy, P., **(2008)** 2'-Lipid-modified oligonucleotides via a 'Staudinger-Vilarrasa' reaction. *Tetrahedron Letters*, 49, (48), 6838.

5/ Invited lectures, oral and posters communications that acknowledge ARO during this reporting time.

1. Philippe Barthélémy, « Hybrid Lipids for Biomedical Applications », *Targeting and Triggering Basic Research*, ARO symposium, 14-16 May (**2012**), University of Cambridge, Cambridge, UK, communication.

2. Philippe Barthélémy, « Multfunctional Nanoplatforms for Biomedical Applications », *NanoSensorPhotonics 2011, Optical Biosensors, Nanobiophotonics and Diagnostics*, Dead Sea, Israel November 5-9, (**2011**), communication.

3. Philippe Barthélémy, « La biodiversité en territoire indigène : Une corne d'abondance pour la découverte de nouveaux médicaments ? », *Indigenous Peoples and the Environment*. Dec. 8,9,10th (**2011**), Bordeaux, France, Invited lecture.

4. Philippe Barthélémy, « Mariage des acides nucléiques avec les lipides : De la chimie moléculaire aux applications biomédicales », *Rotary Club*, L'Isle sur la Sorgue, Décembre 3, (**2011**), France, Conférence invitée.

5. Philippe Barthélémy et al. « NAno-plateforme multifonctionnelle dérivée d'Acides Nucléiques » *Journées Nationales Nanosciences et Nanotechnologies, Colloque* J3N 7-9 novembre (**2011**) - Palais des congrès de Strasbourg, France, Invited communication.

6. Philippe Barthélémy "Smart" synthetic hybrid lipids for biomedical applications », *Biologistes, Chimistes et Physiciens,...aux frontières du vivant*, *BCP-8*, 5th-December (**2011**), Marseille, France, Invited lecture.

7. Barthélémy P. (invited seminar): "Chimie des systèmes Moléculaires et supramoléculaires à visée Biomédicales", 31rst **2011**, Sanofi, Paris, France.

8. Barthélémy P. (invited lecture): « AUTO-ASSEMBLAGES ET APPLICATIONS BIOMÉDICALES » University of Grenoble, 12th April (**2011**), France.

9. Barthélémy P. (invited seminar): "Bioinspired hybrid amphiphiles: when lipids met nucleic acids...", Nucleic acid center (NAC), Odense 15th/06/**2011**, Denmark.

10. A. Aimé, A. Patwa, X. Moreau, L. De Jong, G. Saez, C. Di Giorgio, M. De Méo, Thiéry, I. Bestel P. Barthélémy (poster): ""NANAN" - A multifonctional oligonucleotide-based nanoplatform", SUPRABIO, October **2010**, Bordeaux, CRPP, France.

11. N. Taib, A. Aimé, M. Laguerre, P. Barthélémy, I. Bestel (poster): "Molecular modeling of nucleolipids base-pairing interactions", SUPRABIO, October **2010**, Bordeaux, CRPP, France.

12. Barthélémy P. (invited lecture): « AMPHIPHILES HYBRIDES DÉRIVÉS DE BIOMOLÉCULES: AUTO-ASSEMBLAGES ET APPLICATIONS BIOMÉDICALES » University of Montpellier 2, School of Chemistry 18th November (**2010**), France.

13. Barthélémy P. (invited lecture): "Smart" Lipids for Biomedical Applications, 9th France-Japan Drug Delivery System (DDS) Symposium, 26-29, **2010**. Kumamoto, Japan.

14. Barthélémy, P. (oral communication): « GLYCOSYL-NUCLEOSIDE-LIPID BASED SUPRAMOLECULAR MATERIALS; A "MENAGE A TROIS" FOR BIOMEDICAL APPLICATIONS », XIX International Round Table on Nucleosides, Nucleotides and Nucleic Acids Lyon, France - 29 August - 3 September **2010**.

15. Laetitia De Jong-Moreau, Xavier Moreau, Gladys Saez, Alain Thiéry, Isabelle Betsel, Aime Ahissan, Philippe Barthélémy (poster): "Are nanoparticles encapsulated with nucleolipids safe for freshwater invertebrates?" SUPRABIO, October **2010**, Bordeaux, CRPP, France.

16. Delphine Luvino, Salim Khiati, Frédéric Garzino, Alain Méou, Philippe Barthélémy, Michel Camplo, (poster): "Original cationic nucleoside lipid for gene delivery" SUPRABIO, October **2010**, Bordeaux, CRPP, France.

17. Barthélémy P. (invited lecture): « Hybrid bioinspired amphiphiles: from supramolecular chemistry to biomedical applications » Southampton Supramolecular Chemistry Symposium - 7, 16th July (**2010**), University of Southampton, UK.

18. Barthélémy P. (invited lecture): « NanoBiotechnology/ Nanomedicine », NanoSpain CONF2010, March 26th (**2010**) Malaga, Spain.

19. Barthélémy, P. (oral communication): « Nanostructured materials for drug delivery », Rencontres en Chimie Organique Biologique, (RECOB13) 21-25th March (**2010**), Aussois, France.

20. Barthélémy P. (invited seminar): Nucléolipides ; auto-assemblages et applications biomédicales. Nancy, June (**2010**), Université Henri Poincaré-Nancy I, France.

21. Luvino D., Ceballos, C., Khiati S., Garzino F., Méou A., Barthélémy P., and Camplo, M., (poster) : "Synthèse de nouvelle molecules hybride dérivée de nucleosides amphiphiles cationiques" Rencontres en Chimie Organique Biologique, (RECOB13) 21-25th March (**2010**), Aussois, France.

22. Khiati, S.; Luvino, D.; Oumzil, K.; Pierre, N.; Camplo, M.; Chauffert, B.; Barthélémy, P. (poster): Nanoparticles vectors for drugs delivery - Cancéropôle Grand Sud-Ouest, 1rst July (**2010**), Toulouse, France.

23. K. Oumzil, S. Khiati, P. Barthélémy (poster): Nucléolipides PEG-détachables pour la vectorisation - Cancéropôle Grand Sud-Ouest, 1rst July (**2010**), Toulouse, France.

24. P. Barthélémy (oral communication): “Nanostructured hydrogels for nucleic acid delivery” GTRV- Summer School, « Targeted drug delivery » September 3-4, (**2009**), EPFL (Polydôme), Lausanne, Switzerland.

25. Godeau, G. ; Steadel C. ; Pierre, N. ; Barthélémy, P. : Oligonucléotides lipidiques : Journées Jeunes Chercheurs SCT, Paris, le 5 février **2009**, France

26. Godeau, G.; Bernard, J.; Staedel, C.; Barthélémy, P. Glycosyl-Nucleoside-Lipids as Low molecular weight Gelators. 10th scientific day of the doctoral school sciences of life and health, Arcachon (France), 8 April **2009**, France

27. Godeau, G. ; Steadel C. ; Pierre, N. ; Barthélémy P. : Oligonucléotides amphiphile : un nouvel outil de vectorisation. GTRV, Angers, le 8 décembre **2008**, France

28. Godeau, G. ; Steadel C. ; Pierre, N. ; Barthélémy, P. : Oligonucléotides amphiphile : Journée Scientifique de l'IFR 66, Talence, le 2 décembre **2008**, France

29. Taib N.; Berque-Bestel I.; Laguerre M.; Barthélémy, P. Nucleoside amphiphiles for intracellular delivery of antisenses targeting exon associated with muscular distrophy. GTRV, Angers, le 8 décembre **2008**, France.

30. Gissot A., Diprimo C. ; Berque-Bestel, Giannone G. Chapuis H..; Barthélémy, P. . New biocompatible switch for sensitive liposomes encoded with oligonucleotides amphphiles. GTRV, Angers, le 8 décembre **2008**, France.

31. Chapuis, H.; Bui, Laurent, Pierre, N.; Staedel, C.; Berque-Bestel, I. Barthélémy, P. Ciblage de micorARNs par des oligonucléotides amphiphhiles à visée thérapeutique 4ème journée nationale du Club "Nanomatériaux pour les Sciences du Vivant" intitulée : Vectorisation de Molécules Actives et Ciblage Biologique le 27 mars **2008** à ENSCPB (Bordeaux, France)

32. Bui, L.; Chapuis, H.; Pierre, N.; Staedel, C.; Berque-Bestel, I.; Barthélémy, P. 44e Rencontres Internationales de Chimie Thérapeutique intitulées “*Interfacing Chemical Biology, Natural Products and Drug Discovery*” in Angers (France) on July 2-4, **2008**.

33. S. Khiati, N Campins, N Pierre, P Barthélémy. Club Nanomatériaux pour les sciences du Vivant, 4ème rencontre, Vectorisation de molécules actives et ciblage biologique, Bordeaux 27 mars **2008**, ENSCPB.

34. S. Khiati, N Campins, N Pierre, P Barthélémy. Interface Chimie - Biologie – Physique, 1ère Journée Jeunes Chercheurs, Bordeaux 22 Mai **2008**. IECB.

35. S. Khiati, N Campins, N Pierre, P Barthélémy. Journée Doc's meeting 66, Bordeaux Mardi 24 JUIN, **2008**. ENSCPB.